57. The method of Claim 17 wherein the nitrosated hemoglobin is polynitrosated hemoglobin.

B2 Cont

58. The method of Claim 17 wherein the nitrosated hemoglobin is methemoglobin.

59. A method for inhibiting platelet activation in a mammal, comprising administering to the mammal a composition comprising nitrosated hemoglobin in a therapeutically effective amount.

INTERVIEW SUMMARY

On August 5, 1999, an interview was conducted at the United States Patent and Trademark Office. Carol A. Egner and David E. Brook (Attorneys of Record) and Jonathan S. Stamler, M.D. (Applicant) discussed the application with Bennett Celsa (Patent Examiner).

Example 19 of the Stamler *et al.* patent application WO 93/09806 (which also appears as Example 4 of US 5,380,758 and Example 19 of US 5,593,876) was discussed as it affects the claims. Related applications 08/616,371 filed March 15, 1996, 08/667,003 filed June 20, 1996, and 08/796,164 filed February 6, 1997 were also discussed.

WO 93/09806 was the subject of a Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed with the United States Patent and Trademark Office in ancestor applications 08/616,371 filed March 15, 1996, 08/667,003 filed June 20, 1996, and 08/796,164 filed February 6, 1997. A Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132, accompanied by Exhibits A-H, is being filed concurrently with this Amendment. At the interview, it was explained to Mr. Celsa that Example 19 of WO 93/09806 and Example 1 of U.S. Patent Application No. 08/559,172 (abandoned as of July 6, 1999), both purporting to show synthesis of SNO-hemoglobin, both arose from the same set of experiments performed by Dr. Stamler, even though the accounts of those experiments in the Examples differed in details of the procedure, and both were, in fact, inaccurate in some aspects.

Dr. Stamler elaborated on the statements presented in his Declarations filed in the ancestor applications and in the Declaration being filed concurrently with this Amendment. He explained that the experiment resulting in the spectrum of Figure 28 of WO 93/09806 and Figure

1 of 08/559,172 employed acidified nitrite as the reagent. Although the assay to detect SNO-hemoglobin had been done incorrectly, even had the assay been performed correctly, the products were dissociated hemes and dissociated, denatured subunits. Similar treatment of more acid resistant proteins had resulted in the production of *S*-nitrosoproteins. Figure 29 of WO 93/09806 (Figure 2 of 08/559,172) shows the result of an experiment in which *S*-nitroso-N-acetylcysteine (SNOAc) was added to hemoglobin. Although the description in the Examples recites a different conclusion, the correct conclusion apparent to one of skill in the art is that the spectrum shows that the product contains oxidized hemoglobin, methemoglobin.

As explained in the Declaration of Dr. Stamler, the experimental conditions one might conclude from the Examples were used in an attempt to synthesize SNO-hemoglobin, were tried in more recent experiments in Dr. Stamler's laboratory. Using 12.5 μM SNOAc and 12.5 μM hemoglobin at pH 6.9 did not produce detectable SNO-hemoglobin. See Exhibits E1-E3 accompanying the Declaration of Dr. Stamler.

In future prosecution, Mr. Celsa will be reconsidering the prior art and how it may affect the claims. Specific claim language was not discussed.

REMARKS

Minor corrections are being made to the specification. Among them is a correction on page 67, line 27, which results in low molecular weight *S*-nitrosothiols being accurately described as "trichloric acid *soluble*." It is understood by those of skill in the art that those molecules thought of in biology as being low molecular weight molecules are *acid soluble* and those molecules thought of in biology as being high molecular weight molecules, or macromolecules, are *acid precipitable*. High and low molecular weight molecules are known to be separable by a commonly used acid precipitation procedure.

Claims 1-14 and 18-48 have been canceled. Claim 17 has been amended. Claims 53-59 have been added.

Support for Claims 53 and 56 is found, for instance, on page 41, line 34, to page 42, line 9. Support for Claims 54 and 57 is found on page 38, lines 5-12. See also Example 27, especially page 100, line 16 to page 101, line 11 for a method of synthesis of polynitrosated hemoglobin. Support for Claims 55 and 58 is found in Figure 7C and in Example 9, page 79 line